Kaohsiung Journal of Medical Sciences (2014) 30, 125–132

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Functional connectivity between parietal cortex and the cardiac autonomic system in uremics

Li-Min Liou [a,b], Diane Ruge [a], Mei-Chuan Kuo [c,d], Jer-Chia Tsai [c,d], Che-Wei Lin [e], Meng-Ni Wu [f,g], Chung-Yao Hsu [f,g], Chiou-Lian Lai [f,g,*]

[a] *Sobell Department of Motor Neuroscience and Movement Disorders, University College London–Institute of Neurology, University College London, United Kingdom*
[b] *Department of Neurology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[d] *Faculty of Renal Care, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e] *Department of Electrical Engineering, National Cheng Kung University, Tainan, Taiwan*
[f] *Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[g] *Department of and Master's Program in Neurology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 28 November 2012; accepted 23 September 2013
Available online 11 December 2013

KEYWORDS
Central autonomic network;
Electroencephalography;
Heart rate variability;
Spectral analysis;
Uremia

Abstract Although the central autonomic network (CAN) has been well researched in animal models, the CAN in humans is still unclear, especially for cardiovascular control. This study aimed to investigate which areas of the cerebral cortices are associated with the peripheral cardiac autonomic control involved in the CAN in uremic patients with autonomic dysfunction and normal controls. The central and peripheral autonomic network in 19 uremic patients with significant autonomic dysfunction and 24 age- and sex-matched controls [mean age ± standard deviation (SD), 55.16 ± 10.45 years and 55.42 ± 5.42 years, respectively] were evaluated by simultaneous spectral analysis of electroencephalography (EEG) and electrocardiography recording (ECG), along with serial autonomic tests [autonomic questionnaire and orthostatic blood pressure (BP) change]. Only frequency-domain heart rate variability (f-HRV) during the deep-breathing stage could differentiate the two groups. Although there is no significant

Conflict of Statement: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Department of Neurology, Kaohsiung Medical University Hospital and Department and Master's Program in Neurology, Faculty of Medicine College of Medicine Kaohsiung Medical University, Number 100, Tzyou 1st Road, Sanmin District, Kaohsiung City 807, Taiwan.
E-mail address: lai95069@gmail.com (C.-L. Lai).

http://dx.doi.org/10.1016/j.kjms.2013.11.001

difference in f-HRV during the quiet-breathing stage, different patterns of central oscillation and their correlation with peripheral cardiac autonomic indices could be found for the two groups. Although the power of specific EEG bands under electrode T3 and T6 correlated significantly with the power of peripheral HRV indices in the control group, those under electrodes P3 and Pz had significant correlations in the uremic group suggesting a role of functional connectivity between them. In addition, sympathetic activity is correlated with slow wave EEG (theta/delta) power whereas parasympathetic activity is correlated with fast wave EEG (beta) power. In conclusion, there is functional connectivity between the parietal cortex and the peripheral cardiac autonomic system (PAN) in uremics and the pattern of central autonomic connectivity differs between uremic patients with autonomic dysfunction and normal controls.

Introduction

Through the purported central autonomic network (CAN), the brain can significantly affect autonomic outflow and manage afferent—efferent integration of the autonomic nervous system [1]. The neuroanatomy of the CAN has been well described in animal models: afferent autonomic inflow is carried via cranial, sacral, and thoracolumbar nervous pathways to the nucleus in the medulla, pons, thalamus, and subsequently hypothalamus, amygdala, or insula. Efferent autonomic outflow, which are mainly from the medulla, can also be modulated by both afferent autonomic inflow and central command from a set of regions including the rostral ventromedial medulla, midbrain periaqueductal gray, hypothalamus, amygdala, and dorsomedial prefrontal and anterior cingulate cortices [1].

Although the medulla oblongata is regarded as the primary cardiac autonomic center, recent animal studies have highlighted that certain cerebral cortices, such as insular cortex and anterior cingulate cortex, the amygdala, and the cerebellum are involved with the modulation of cardiovascular control [2]. However, studies on connectivity between the CAN and the peripheral cardiac autonomic system (PAN) in humans were still limited. One author reported that electrical stimulation of the insular cortex, anterior cingulate cortex, and medial temporal lobe leads to changes in blood pressure (BP) and heart rate (HR) giving clues that there is effective connectivity between certain cerebral cortices and the PAN [2]. Napadow et al. [1] used a combined functional magnetic resonance imaging (fMRI) and heart rate variability (HRV) method to investigate the connectivity between the CAN and the PAN in humans. They reported that powers of high frequency (HF) correlates with fMRI activity in the hypothalamus, cerebellum, parabrachial nucleus/locus ceruleus, periaqueductal gray, amygdala, hippocampus, thalamus, and dorsomedial/dorsolateral prefrontal, posterior insular, and middle temporal cortices indicating that there is functional connectivity between the CAN and the PAN. Although some regions are consistent with those in animal models, other mostly higher cortical or limbic-related brain regions may be unique to humans [1]. However, this type of research is expensive and a special cardiac-gated fMRI technique is essential.

Since 1960, some electroencephalography (EEG) studies have found that there are connections between brain activity and the PAN [3]. In 2005, Takahashi et al. [4] also found that there are correlations between changes in EEG band power and frequency-domain HRV (f-HRV) indices during meditation. Because f-HRV represents PAN function, the brain areas that have significant correlation between quantitative EEG power and f-HRV indices (central link pattern) may represent their CAN and its link to the PAN. Autonomic dysfunction is an important issue in uremic patients [5] because it occurs in 66% of uremic patients and is regarded as one of the possible mechanisms of increased cardiovascular mortality [6,7]. However, the CAN in uremics with autonomic dysfunction and its connection to the PAN is not clear. We hypothesized that there is functional connectivity between the cerebral cortex and the PAN in uremics and that the pattern of central autonomic connectivity differs between uremic patients with autonomic dysfunction and controls. In the literature, most simultaneous spectral analysis of EEG and ECG studies used only a small number of electrodes to study brain activity. There are no studies focusing on uremic patients. The present study aimed to assess which cerebral cortices are associated with the PAN in uremic patients and healthy controls.

Patients and methods

Participants

Participants were consecutively recruited from Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan. The uremic group consisted of 19 participants [mean age $\pm$ standard deviation (SD), 55.16 $\pm$ 10.45 years; female-to-male ratio: 9/10] with regular bicarbonate hemodialysis (for 4 hours thrice weekly). Patients with conditions known to affect cardiac and peripheral sensorimotor functions, such as diabetes mellitus, amyloidosis or alcoholism, history of arrhythmia, severe heart failure, ischemic heart disease, or broncho-pneumopathy were excluded. Patients with central nervous system diseases, such as Parkinson's disease and cerebrovascular disease were also excluded. None of the patients were taking medications acting on the autonomic nervous system, including beta-blockers, benzodiazepines, etc.

Twenty-four age- and sex-matched controls (mean age $\pm$ SD, 55.42 $\pm$ 5.42 years; female-to-male ratio: 18/6) were recruited from the hospital and local community.

They were carefully screened to ensure they had no history or disease treatment affecting peripheral sensorimotor and autonomic functions. All participants in both groups underwent an assessment of autonomic function and simultaneous EEG and ECG recordings after signed informed consent was given.

Each participant was asked to refrain from smoking and drinking coffee for at least 12 hours, and not to exercise for 24 hours prior to the experiment, and to refrain from eating and drinking for at least 3 hours prior to the examination. The examinations were performed during the same time period of the day (from 10 AM to 12 PM). The uremics were examined on a dialysis-free day. The patients were initially asked to complete an autonomic questionnaire, which included two items related to the cardiovascular system: palpitations and orthostatic dizziness. The answer to each item was either "Yes" or "No". They were then instructed to lie in the supine position on a bed in a quiet and electrically shielded room with the temperature around 25 °C. They were asked to be relaxed and think about nothing. After 10 minutes, a bedside cardiovascular reflex test for orthostatic systolic BP change was performed [8]. The test of predominantly sympathetic function was BP response to active standing. After completing the test, each participant had a 10-minute rest in the supine position.

EEG and ECG electrodes were then attached and simultaneous recordings were performed. Each participant was asked to perform two stages: closed eyes with quiet breathing for 5 minutes, followed by deep breathing for another 5 minutes. After another 2 minutes, the examination was complete. The local institutional review board approved all study protocols.

Simultaneous EEG and ECG recording and analysis

The EEG activity was recorded using nineteen electrodes (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, O1, and O2) according to the International 10-20 System, referenced to linked ear lobe electrodes. The EEG activity was recorded using a Nicolet monitor (Alliance 226, Nicolet; Madison, Wisconsin, USA) digitized at 1024 Hz with a low filter at 1 Hz and high filter at 70 Hz (decay constant 12 dB). Impedance was less than 10 kV for each electrode. EEG signals (sampling frequency, 500 Hz) were recorded with a time constant of 0.1 second and a sensitivity of 7 μV/mm. The data were simultaneously stored on a magnetic optical disk for offline analysis.

Two ECG electrodes were placed on either side of the heart in front of the chest to record the electrical activity of the heart over time. The EEG and ECG recordings were made simultaneously.

The Matlab software (version 7.12) was used to detect and analyze the EEG and ECG channels. In the EEG channels, artifacts due to eyeball, body movements, swallowing, and drowsiness were excluded from the analysis. The power spectrum of delta (0.3—4 Hz), theta (4—8 Hz), alpha (8—13 Hz), and beta (13—30 Hz) bands during approximately 5 minutes of quiet breathing and 5 minutes of deep breathing were then obtained by Fast Fourier transformation. The power spectrum of alpha, beta, theta, and delta were then transferred to alpha percentage (alpha power/total power), beta percentage (beta power/total power), theta percentage (theta power/total power), and delta percentage (delta power/total power) to decrease the influence of the small difference in analysis time.

In the ECG channel, the recording time was a constant for 5 minutes. We used the method designed by Lin et al. [9] to analyze HRV. The QRS complexes were detected and labeled automatically. The results of the automatic analysis were reviewed subsequently and any errors in R-wave detection and QRS labeling were then edited manually. HRV was assessed automatically by the monitor from the calculation of the mean R—R interval and its SD measured on consecutive 5 minutes ECG. Normal-to-normal R—R interval data obtained from the edited time sequence of R-wave and QRS labeling were then transferred to a personal computer.

There were two ways to express LF (low frequency) and HF (high frequency): absolute values (ms^2) and relative values (normalized units: LF nu and HF nu). After Fast Fourier transformation, the frequency-domain parameters selected were LF (power spectrum between 0.04 Hz and 0.15 Hz), HF (power spectrum between 0.15 Hz and 0.40 Hz), and VLF (very low frequency; power spectrum below 0.04 Hz). The LF and HF components were obtained in absolute values of power (ms^2). The values of LF nu and HF nu, which represented the relative value of the power of each component in proportion to the total power minus the VLF component, were then obtained. Normalized units tended to minimize the effect of the change in total power on the values of LF and HF components, and could better provide the balance and integration of sympathetic and parasympathetic modulation. These parameters were defined in accordance with the 1996 the American College of Cardiology (ACC)/the American Heart Association (AHA)/the European Society of Cardiology (ESC) consensus [10]. In line with this, the LF nu and HF nu were chosen as parameters to find the balance of sympathetic and parasympathetic modulation and the correlation with the percentage of alpha, beta, theta, and delta EEG power, respectively.

Statistical analysis

Statistical analyses were conducted using the JMP software for Windows (version 8.02). The power spectrum values were expressed as mean ± SD. Statistical comparisons of the results were made using the Student t test. When comparing symptoms suggestive of autonomic dysfunction, baseline HR, orthostatic BP change, quiet-breathing and deep-breathing LF nu and HF nu between the uremic and control groups, significance levels were set at $p < 0.05$. When comparing percentage of alpha, beta, theta, and delta EEG power between the uremic and control groups in quiet-breathing and deep-breathing, we used the Bonferroni strategy of multiple comparisons (19 EEG electrodes) to Type I error rate of significant factors by dividing 0.05 by 19, and significance levels were set at $p < 0.00263$. The association between the percent change of EEG power and HRV indices was analyzed using a multivariate regression test with repeated measurements on percentage of alpha, beta, theta, and delta EEG power,

and LF nu and HF nu. Unless otherwise specified, significance was set at $p < 0.05$.

Results

Autonomic questionnaire between uremic and control groups

The uremic group showed significantly more symptoms of orthostatic dizziness ($p = 0.00007$) and palpitations ($p = 0.0024$) compared to the control group, indicating autonomic dysfunction (Table 1).

Differences in f-HRV indices between the uremic and control groups during quiet- and deep-breathing stages

By means of f-HRV and using LF nu and HF nu as parameters, there were no significant differences in LF nu and HF nu between the two groups during the quiet-breathing stage ($p = 0.1031$; Table 1). However, during the deep-breathing stage, the uremic group had significantly higher HF nu (lower LF nu; $p = 0.0014$).

Electrodes with significant differences in percentage of alpha, beta, theta, and delta EEG power on the International 10-20 System during quiet- and deep-breathing stages

The percentage of alpha, beta, theta, and delta EEG power at different electrodes between the two groups during quiet- and deep-breathing stages were compared (Table 2). During the quiet-breathing stage, the uremic group had a significantly lower percentage of alpha EEG power at the F3, Cz, C3, C4, and T3 electrodes ($p = 0.0017$, $p = 0.0005$, $p = 0.0009$, $p = 0.0007$, and $p = 0.0024$, respectively) compared to the control group. The uremic group had a significantly higher percentage of delta EEG power at the F3, Cz, C3, C4, Pz, and P3 electrodes ($p = 0.0024$, $p = 0.0004$, $p = 0.0013$, $p = 0.0002$, $p = 0.0002$, and $p = 0.0001$, respectively) compared to the control group.

During the deep-breathing stage, the uremic group had a significantly lower percentage of alpha EEG power at the F4, Cz, C3, C4, T3, Pz, and P3 electrodes ($p = 0.0026$, $p < 0.0001$, $p < 0.0001$, $p < 0.0001$, $p = 0.0018$, $p = 0.0007$, and $p = 0.0007$, respectively). The uremic group had a significantly higher percentage of delta EEG

Table 2 Electrodes with significant differences in alpha, beta, theta, and delta electroencephalography (EEG) power on the International 10-20 System during quiet- and deep-breathing stages.

	Quiet-breathing stage		Deep-breathing stage	
	Electrode	*p*	Electrode	*p*
Alpha[a]	F3	0.0017	F4	0.0026
	Cz	0.0005	Cz	<0.0001
	C3	0.0009	C3	<0.0001
	C4	0.0007	C4	<0.0001
	T3	0.0024	T3	0.0018
	—	—	Pz	0.0007
	—	—	P3	0.0007
Beta[a]	—	—	—	—
Theta[a]	—	—	—	—
Delta[a]	F3	0.0024	F4	0.0026
	Cz	0.0004	Cz	<0.0001
	C3	0.0013	C3	0.0005
	C4	0.0002	C4	0.0003
	Pz	0.0002	P3	<0.0001
	P3	0.0001	P4	0.0003
			Pz	<0.0001

[a] By Student *t* test, Bonferroni strategy of multiple comparisons.

Table 1 Demographic data, clinical characteristics, heart rate variability (HRV) indices, and central sympathetic correlation ratio in the uremic and control groups.

	Uremics ($n = 19$)	Control ($n = 24$)	*p*
	Mean ± SD	Mean ± SD	
Age[a] (y)	55.16 ± 10.45	55.42 ± 5.42	0.92
Sex[b] (male/female)	10/9	6/18	0.062
Palpitation[b]	11	4	**0.0024**
Orthostatic dizziness[b]	12	2	**0.00007**
Baseline heart rate[a] (beats/min)	73.05 ± 2.37	66.71 ± 2.11	0.052
Orthostatic SBP change[a]	12.00 ± 17.84	8.00 ± 8.51	0.338
Quiet-breathing stage			
LF nu[a]	43.33 ± 25.97	55.28 ± 22.17	0.1031
HF nu[a]	56.67 ± 25.97	44.73 ± 22.17	0.1031
Deep-breathing stage			
LF nu[a]	73.30 ± 25.26	91.25 ± 4.89	**0.0014**
HF nu[a]	26.70 ± 25.26	8.75 ± 4.89	**0.0014**

HF nu = normalized unit of high frequency power; LF nu = normalized unit of low frequency power; RRIV = variability of RR interval; SBP = systolic blood pressure; SD = standard deviation.
The values that appear in bold font indicates $p < 0.05$.
[a] Student *t* test.
[b] χ^2 test.

Table 3 Electrodes with significantly positive correlation between electroencephalography (EEG) power and sympathetic/parasympathetic activity in the uremic and control groups.

	Alpha		Beta		Theta		Delta	
	Control (r, p)	Uremia (r, p)	Control (r, p)	Uremia (r, p)	Control (r, p)	Uremia (r, p)	Control (r, p)	Uremia (r, p)
Quiet-breathing stage								
LF nu[a] (sym)	ns	ns	ns	Pz (−0.53, 0.0206)	T3 (+0.44, 0.0316) T6 (+0.41, 0.0467)	ns	ns	P3 (+0.52, 0.0236) Pz (+0.57, 0.0112)
HF nu[a] (para)	ns	ns	ns	Pz (+0.53, 0.0206)	T3 (−0.44, 0.0316) T6 (−0.41, 0.0467)	ns	ns	P3 (−0.52, 0.0236) Pz (−0.57, 0.0112)
Deep-breathing stage								
LFnu[a] (sym)	ns	Fz (+0.49, 0.023)	ns	C3 (−0.50, 0.020) C4 (−0.52, 0.016) F7 (−0.50, 0.019) F8 (−0.52, 0.015)	T4 (+0.43, 0.034)	ns	ns	ns
HF nu[a] (para)	ns	Fz (−0.49, 0.023)	ns	C3 (+0.50, 0.020) C4 (+0.52, 0.016) F7 (+0.50, 0.019) F8 (+0.52, 0.015)	T4 (−0.43, 0.0343)	ns	ns	ns

+ = positive correlation; − = no significant correlation; HF nu = normalized unit of high frequency power; LF nu = normalized unit of low frequency power; ns = no significant correlation; para = parasympathetic activity; sym = sympathetic activity.
[a] By multivariate, pair-wise correlations.

power at the F4, Cz, C3, C4, P3, P4, and Pz electrodes ($p = 0.0026$, $p < 0.0001$, $p = 0.0005$, $p = 0.0003$, $p < 0.0001$, $p = 0.0003$, and $p < 0.0001$, respectively).

Compared to the quiet-breathing stage, there are relative higher percentages of alpha and beta EEG power and relatively lower percentages of theta and delta EEG power both in control and uremic groups during the deep-breathing stage. However, there is no significant difference (Table 2).

Electrodes with significant correlation between power of LF nu (sympathetic activity) and HF nu (parasympathetic activity) and percentage of alpha, beta, theta, and delta EEG power

Multivariate regression analysis was used to test the relationship between the percentage of alpha, beta, theta, and delta EEG power and HRV indices with repeated measurements. In the quiet-breathing stage, in the control group, there were significantly positive correlations between LF nu (negative correlations between HF nu) and percentage of theta EEG power at the T3 ($p = 0.0316$) and T6 ($p = 0.0467$) electrodes. In the uremic group, there were significantly positive correlations between LF nu (negative correlations between HF nu) and percentage of delta EEG power at the P3 ($p = 0.0236$) and Pz ($p = 0.0112$) electrodes and positive correlations between HF nu (negative correlations between LF nu) and percentage of beta EEG power at the Pz ($p = 0.0206$) electrode (Table 3).

In the deep-breathing stage, in the control group, there were significantly positive correlations between the LF nu (negative correlations between the HF nu) and percentage of theta EEG power at the T4 ($p = 0.034$) electrode. In the uremic group, there were significantly positive correlations between HF nu (negative correlations between LF nu) and percentage of beta EEG power at the C3, C4, F7, and F8 ($p = 0.020$, $p = 0.016$, $p = 0.019$, and $p = 0.015$, respectively) electrodes; significantly positive correlations between LF nu (negative correlations between HF nu) and percentage of alpha EEG power at the Fz ($p = 0.023$) electrode (Table 3).

When LF nu was used as sympathetic modulation and HF nu as parasympathetic modulation [11], local EEG power under electrodes that have correlations with power of LF nu or HF nu were regarded as brain areas having central sympathetic or parasympathetic modulations (CAN). These are shown in Table 3.

In summary, during the quiet-breathing stage, while the power of specific EEG bands under electrodes T3 ($p = 0.0316$) and T6 ($p = 0.0467$; temporal cortex) had significant correlation with the power of peripheral HRV indices in the control group (Fig. 1A), those under electrodes P3 ($p = 0.0236$) and Pz ($p = 0.0112$; extratemporal cortex) had significant correlation with the power of peripheral HRV indices in the uremic group (Fig. 1B). During the deep-breathing stage, while the power of specific EEG bands under electrodes T4 ($p = 0.034$) had significant correlation with the power of peripheral HRV indices in the control group (Fig. 1C), those under electrodes C3, C4, F7, F8, and Fz ($p = 0.020$, 0.016, 0.019, 0.015, and 0.023, respectively) had significant correlation with the power of peripheral HRV indices in the uremic group (Fig. 1D).

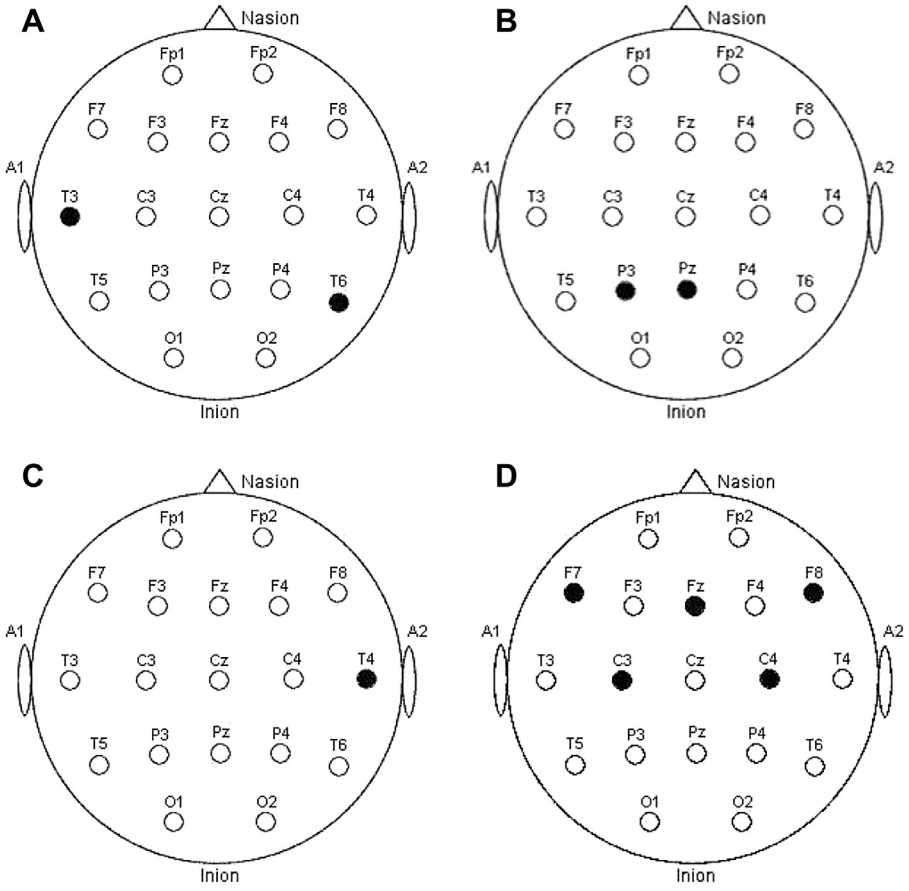

Figure 1. During the quiet-breathing stage, (A) there were significant correlations between HRV indices and specific EEG band power at the T3 and T6 electrodes in the control group; (B) significant correlations between HRV indices and specific EEG band power at the Pz and P3 electrodes in the uremic group. During the deep-breathing stage, (C) there were significant correlations between HRV indices and specific EEG band power at the T4 electrodes in the control group; (D) significant correlations between HRV indices and specific EEG band power at the C3, C4, Fz, F7, and F8 electrodes in the uremic group. EEG = electroencephalography; HRV = heart rate variability.

Discussion

The present study demonstrates functional connectivity between the parietal cortex and the PAN in uremics and the pattern of central autonomic connectivity differs between uremic patients and healthy controls. Although HRV indices cannot differentiate uremic patients from controls during the quiet-breathing stage, different patterns of central connectivity between these two groups can be observed. This is the first study to investigate the integration of the CAN and the PAN by means of spectral analysis of simultaneous EEG and ECG recordings in uremic patients.

The role of the cerebral cortex in the modulation of autonomic function becomes more and more important because long-term potentiation can be induced in the human brain by the technique of transcranial magnetic stimulation [12]. The quantitative EEG is used to investigate the activity of the cerebral cortex because of its better temporal resolution from variable electrophysiological and hemodynamic methods. It can help for diagnosis and predict prognosis in clinical settings, such as Alzheimer's disease [13,14]. In our study, during the quiet-breathing stage, there were significantly positive correlations between LF nu and percentage of theta EEG power in the control group, whereas there were significantly positive correlations between LF nu and percentage of delta EEG power and between HF nu and percentage of beta EEG power in the uremic group. Sympathetic activity (LF nu) seems to correlate with slow wave EEG power: theta in control, and delta in uremics. These results are similar as in some animal studies [15,16]. Parasympathetic activity (HF nu) seems to correlate with fast wave EEG power: beta in uremics. No similar results have been reported previously for this. The significance of alpha, beta, theta, and delta rhythm are different in various physiological conditions. For example, although alpha waves are generally related to the condition of "relaxed wakefulness", frontocentral alpha waves can possibly reflect sleep-maintaining processes [17]. Although theta waves are prominent in non-rapid eye movement (NREM) sleep [18], frontal theta rhythm is related to the meditation state [4]. Whether parasympathetic or sympathetic impairment is prominent in uremic patients remains controversial [19]: although some authors favor more sympathetic impairment [20], others favor more parasympathetic damage or both [19]. These may be due to different methodologies. The uremics in our study had

significantly lower LF nu than the control group during the deep-breathing stage (Table 1), suggesting more sympathetic impairment in uremic patients.

The "deep-breathing" test is used because it is actually an effective autonomic challenge test for differentiating pathologic conditions, such as differentiating Parkinson's disease (PD) from multiple system atrophy (MSA) patients [21]. This may explain why there were only significant differences in the HRV indices during deep-breathing stages in our study, although more orthostatic dizziness and palpitations were found in the uremic group ($p < 0.05$). In our study, we found that the deep-breathing maneuver changed the power of HRV indices significantly, whereas it did not change EEG power. These may explain why the cerebral cortices that are functionally connected with the cardiac autonomic system differ between quiet- and deep-breathing stages.

The CAN is complex. In recent years, there has been increasing evidence supporting the role of frontal, temporal, and parietal cerebral cortex [22] in the CAN of humans. For example, infarctions involving the parietal lobe seem to be associated with a particularly increased risk of cardiac events and death [23]. Lateralization, lesion size-specific, and disease-specificity [23—26] are also important issues in the CAN. Autonomic responses of lateralized lesions have been shown to be opposite between stroke and epileptic patients [24,25]. In stroke patients the left prefrontal cortex lesions result in decreased cardiovascular responses to visual emotional stimuli [25], whereas in epilepsy patients during the Wada test, left-hemispheric inactivation increases sympathetic cardiovascular modulation [24]. Min et al. [26] further demonstrated that left focal insular ischemia that induced cardiac dysfunction was related to the extent of insular cortical injury. These factors may explain why P3 and Pz are involved in the CAN in uremics with autonomic dysfunction.

The capacity of the nervous system to reorganize (plasticity) is of fundamental importance for recovery from brain injury [27]. In Parkinson's disease patients, to facilitate complex finger movements, there is a switch from the use of the striato-mesial frontal to the parietal-lateral premotor circuits [28]. The present study shows similar results in uremic patients with autonomic dysfunction. There is a switch from the use of temporal areas (T3, T6) to parietal areas (P3, Pz) in the uremics with autonomic dysfunction (Fig. 1).

This study has some limitations. First, the EEG has no accurate anatomical specificity due to the filter function of the skull. However, its strength lies in the superior temporal discrimination and it can detect functional connectivity of brain activity and HRV. Electrocorticography (ECoG) can provide more accurate EEG power but is an invasive technique inappropriate for routine clinical use. Multimodal neuroimaging studies combining EEG and imaging could provide a possible way to resolve this problem in future studies [29]. Second, like Ako et al.'s method [18], we correlated data from pairs of 5-minute HRV indices and EEG spectral power. Because these are not real-time physiological results, the temporal relationship between EEG and HRV may be compromised. However, a 5-minute f-HRV recording is essential in the diagnosis and quantification of dysfunction in the PAN [20]. At least we can say there is correlation between EEG and HRV during the same 5-minute time period.

In conclusion, there is functional connectivity between the parietal cortex and the PAN in uremics and the pattern of central autonomic connectivity differs between uremic patients with autonomic dysfunction and normal controls.

Acknowledgments

This study was supported by a grant from Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan (kmhk-93-006). The authors appreciate assistance from the Statistical Analysis Laboratory, Department of Clinical Research, Kaohsiung Medical University Hospital.

References

[1] Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. Neuroimage 2008;42:169—77.
[2] Kimmerly DS, O'Leary DD, Menon RS, Gati JS, Shoemaker JK. Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. J Physiol 2005;569:331—45.
[3] Van Buren JM, Ajmone-Marsan C. A correlation of autonomic and EEG components in temporal lobe epilepsy. Arch Neurol 1960;3:683—703.
[4] Takahashi T, Murata T, Hamada T, Omori M, Kosaka H, Kikuchi M, et al. Changes in EEG and autonomic nervous activity during meditation and their association with personality traits. Int J Psychophysiol 2005;55:199—207.
[5] Robinson TG, Carr SJ. Cardiovascular autonomic dysfunction in uremia. Kidney Int 2002;62:1921—32.
[6] Levin A. Anemia and left ventricular hypertrophy in chronic kidney disease populations: a review of the current state of knowledge. Kidney Int Suppl 2002;80:35—8.
[7] Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial 2008;21:300—7.
[8] Vita G, Princi P, Calabro R, Toscano A, Manna L, Messina C. Cardiovascular reflex tests. Assessment of age-adjusted normal range. J Neurol Sci 1986;75:263—74.
[9] Lin CW, Wang JS, Chung PC. Mining physiological conditions from heart rate variability analysis. Comput Intell 2010;5:50—8.
[10] Cavalcanti S, Chiari L, Severi S, Avanzolini G, Enzmann G, Lamberti C. Parametric analysis of heart rate variability during hemodialysis. Int J Biomed Comput 1996;42:215—24.
[11] Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am Heart J 1994;127:1376—81.
[12] Cooke SF, Bliss TV. Plasticity in the human central nervous system. Brain 2006;129:1659—73.
[13] Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004;115:1490—505.
[14] Wan B, Ming D, Fu X, Yang C, Qi H, Chen B. Study on a quantitative electroencephalography power spectrum typical of Chinese Han Alzheimer's disease patients by using wavelet transforms. J Neural Eng 2006;3:71—7.
[15] Camerer H, Stroh-Werz M, Krienke B, Langhorst P. Postganglionic sympathetic activity with correlation to heart rhythm and central cortical rhythms. Pflugers Archiv 1977;370:221—5.
[16] Kenney MJ, Gebber GL, Barman SM, Kocsis B. Forebrain rhythm generators influence sympathetic activity in anesthetized cats. Am J Physiol 1990;259:572—8.
[17] Ehrhart J, Toussaint M, Simon C, Gronfier C, Luthringer R, Brandenberger G. Alpha activity and cardiac correlates: three

types of relationships during nocturnal sleep. Clin Neurophysiol 2000;111:940—6.
[18] Ako M, Kawara T, Uchida S, Miyazaki S, Nishihara K, Mukai J, et al. Correlation between electroencephalography and heart rate variability during sleep. Psychiatry Clin Neurosci 2003;57:59—65.
[19] Vita G, Bellinghieri G, Trusso A, Costantino G, Santoro D, Monteleone F, et al. Uremic autonomic neuropathy studied by spectral analysis of heart rate. Kidney Int 1999;56:232—7.
[20] Rubinger D, Sapoznikov D, Pollak A, Popovtzer MM, Luria MH. Heart rate variability during chronic hemodialysis and after renal transplantation: studies in patients without and with systemic amyloidosis. J Am Soc Nephrol 1999;10:1972—81.
[21] Holmberg B, Kallio M, Johnels B, Elam M. Cardiovascular reflex testing contributes to clinical evaluation and differential diagnosis of Parkinsonian syndromes. Movement Disorders 2001;16:217—25.
[22] Zhang Z, Oppenheimer SM. Characterization, distribution and lateralization of baroreceptor-related neurons in the rat insular cortex. Brain Res 1997;760:243—50.
[23] Hilz MJ, Schwab S. Stroke-induced sudden-autonomic death: areas of fatality beyond the insula. Stroke 2008;39:2421—2.
[24] Hilz MJ, Dutsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol 2001;49:575—84.
[25] Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. Neurology 2001;57:833—8.
[26] Min J, Farooq MU, Greenberg E, Aloka F, Bhatt A, Kassab M, et al. Cardiac dysfunction after left permanent cerebral focal ischemia: the brain and heart connection. Stroke 2009;40:2560—3.
[27] Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science 1996;272:1791—4.
[28] Samuel M, Ceballos-Baumann AO, Blin J, Uema T, Boecker H, Passingham RE, et al. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 1997;120:963—76.
[29] Valdes-Sosa PA, Kotter R, Friston KJ. Introduction: multimodal neuroimaging of brain connectivity. Philos Trans R Soc Lond B Biol Sci 2005;360:865—7.